Detection rate and localization of prostate cancer recurrence using Ga-PSMA-11 PET/MRI in patients with low PSA values 0.5 ng/ml

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Abstract: A first analysis of simultaneous Ga-PSMA-11 PET/MRI showed some improvement in the detection of recurrent disease at low serum prostate specific antigen (PSA) values below 0.5 ng/ml compared to the already high detection rate of Ga-PSMA-11 PET/CT. We therefore focused on all patients with biochemical recurrence (BR) and PSA values 0.5 ng/ml to assess the detection rate for Ga-PSMA-11 PET/MRI. We retrospectively analyzed a cohort of 66 consecutive patients who underwent a Ga-PSMA-11 PET/MRI for BR with a PSA value 0.5 ng/ml at our institution. Median PSA level was 0.23 ng/ml (range: 0.03 - 0.5 ng/ml). Detection of PSMA-positive lesions within the prostate fossa, local and distant lymph nodes, bones or visceral organs was recorded. In addition, all scans with Ga-PSMA-11 PET/MRI positive lesions were retrospectively assessed to analyze if lesions were detected inside or outside of a standard salvage radiotherapy volume. Overall, in 36 of 66 patients (54.5%) PSMA-positive lesions were detected; in 26 of 40 (65%) patients with a PSA between 0.2 - 0.5 ng/ml and in 10 of 26 (38.5%) patients with a PSA < 0.2 ng/ml. Even at those low PSA values, only 8 of 66 (12.1%) patients had exclusive local recurrence. In 23 patients lymph nodes and in 5 patients bone metastases were detected on Ga-PSMA-11 PET/MRI. In 26 of 66 patients (39.4%) PSMA-positive lesions were located outside a standard salvage radiotherapy volume. Our data confirm that Ga-PSMA-11 PET/MRI has a high detection rate for recurrent prostate cancer, even at low PSA levels 0.5 ng/ml. In addition, we show that Ga-PSMA-11 PET/MRI detected PSMA-positive lesions outside a standard salvage radiotherapy volume in 39.4% of all patients.

DOI: https://doi.org/10.2967/jnumed.118.225276

Detection rate and localization of prostate cancer recurrence using ^{68}Ga-PSMA-11 PET/MRI in patients with low PSA values ≤ 0.5 ng/ml.

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Running title: ^{68}Ga-PSMA-11 PET/MRI

Manuscript details:

# of words abstract:	277
# of words manuscript:	3361
# of pages:	27
# of tables:	3
# of figures:	4

ABSTRACT

Purpose: A first analysis of simultaneous ^{68}Ga-PSMA-11 PET/MRI showed some improvement in the detection of recurrent disease at low serum prostate specific antigen (PSA) values below 0.5 ng/ml compared to the already high detection rate of ^{68}Ga-PSMA-11 PET/CT. We therefore focused on all patients with biochemical recurrence (BR) and PSA values ≤ 0.5 ng/ml to assess the detection rate for ^{68}Ga-PSMA-11 PET/MRI.

Methods: We retrospectively analyzed a cohort of 66 consecutive patients who underwent a ^{68}Ga-PSMA-11 PET/MRI for BR with a PSA value ≤ 0.5 ng/ml at our institution. Median PSA level was 0.23 ng/ml (range: 0.03 – 0.5 ng/ml). Detection of PSMA-positive lesions within the prostate fossa, local and distant lymph nodes, bones or visceral organs was recorded. In addition, all scans with ^{68}Ga-PSMA-11 PET/MRI positive lesions were retrospectively assessed to analyze if lesions were detected inside or outside of a standard salvage radiotherapy volume.

Results: Overall, in 36 of 66 patients (54.5%) PSMA-positive lesions were detected; in 26 of 40 (65%) patients with a PSA between 0.2 - 0.5 ng/ml and in 10 of 26 (38.5%) patients with a PSA < 0.2 ng/ml. Even at those low PSA values, only 8 of 66 (12.1%) patients had exclusive local recurrence. In 23 patients lymph nodes and in 5 patients bone metastases were detected on ^{68}Ga-PSMA-11 PET/MRI. In 26 of 66 patients (39.4%) PSMA-positive lesions were located outside a standard salvage radiotherapy volume.

Conclusion: Our data confirm that ^{68}Ga-PSMA-11 PET/MRI has a high detection rate for recurrent prostate cancer, even at low PSA levels ≤ 0.5 ng/ml. In addition, we show that ^{68}Ga-PSMA-11 PET/MRI detected PSMA-positive lesions outside a standard salvage radiotherapy volume in 39.4% of all patients.

Key words (MESH-keywords): Prostate Cancer, Prostate-Specific Antigen, ^{68}Ga-PSMA-11, Positron Emission Tomography, PSMA Antigen

INTRODUCTION

Salvage radiotherapy (sRT) to the prostatic bed is still the only localized treatment option for patients with biochemical recurrence (BR) following radical prostatectomy. Early sRT, in patients treated before PSA levels rise to > 0.5 ng/ml, will achieve undetectable PSA levels in more than 60% of the patients, while providing a 80% change of 5-year progression-free survival (*1*). Yet, for those 30% of patients without any effect on PSA levels due to extrapelvic localization of the recurrence, sRT to the prostatic bed is of limited value (*2*).

Detection rates of choline positron emission tomography / computerized tomography (PET/CT) range only between 5 - 24% in patients with BR and PSA levels < 1 ng/mL following radical prostatectomy (*3*). In contrast, a recent meta-analysis demonstrated a detection rate of 45% (95% confidence interval 39 - 52%) using the new ^{68}Gallium labeled PET tracer targeting the prostate specific membrane antigen (PSMA) in patients with BR and PSA values of 0.2 – 0.49 ng/ml (*4*). PSMA-based targeted radiotherapy might therefore become a therapeutic option in patients with BR (*5,6*). However, data about the oncological outcome of PSMA-based targeted radiotherapy is still limited and ongoing clinical trials have to be completed before definitive conclusions regarding the effect of targeted salvage treatments can be drawn (*7*). The superior soft tissue contrast of PET/MRI might further improve the detection of pelvic lesions and indeed first preliminary results for ^{68}Ga-PSMA-11 PET/MRI showed that especially in patients with very low PSA values, the detection rate was higher compared to the published results for PET/CT (*8*). However, this was based on a small patient number. Hence, robust results for the performance of PET/MRI in patients with very low PSA values are still missing.

Furthermore, several studies showed that even at low PSA values, the detected lesions are not exclusively localized in the prostatic bed. In these cases an adaption of the target volume of sRT can be discussed. However, it has not been analyzed yet in how many cases ^{68}Ga-PSMA-11 PET/MRI would possibly lead to a change or modification (e.g. with additional boost) of the target volume compared to a “classical” sRT to the prostate bed, as performed when macroscopic tumor is not detectable in patients with low PSA values. We aimed to analyze the detection rate of ^{68}Ga-PSMA-11 PET/MRI in patients with BR after radical prostatectomy and low PSA values ≤ 0.5 ng/ml. In addition, we aimed to retrospectively assess if lesions detected by ^{68}Ga-PSMA-11 PET/MRI were detected outside a standard sRT volume.

MATERIALS AND METHODS

Patients

We retrospectively analyzed all patients who received ^{68}Ga-PSMA-11 PET/MRI for BR after radical prostatectomy at low PSA values ≤ 0.5 ng/ml scanned between April 2016 and December 2017 at our department. BR was confirmed in all patients by at least two consecutive PSA values. Patients with very low PSA values < 0.2 ng/ml were also included in the present analysis. The local ethics committee approved the study protocol (BASEC Nr. 2016-02230) and all patients had given a general written informed consent. Twenty patients from the previously published cohort investigating the detection rate of ^{68}Ga-PSMA-11 PET/MRI for all PSA values were included in the present data set (*8*). Clinical parameters including PSA, primary tumor stage, Gleason score and surgical margin status were assessed. The detection rate of PSMA-positive lesions was analyzed overall and for 2 subgroups: very low PSA (0 - < 0.2 ng/ml) and low PSA (0.2 – 0.5 ng/ml). Further, the region of detection was assessed (prostatic fossa (including bed of seminal vesicles), pelvic, para-aortic, mediastinal/supraclavicular and axillary lymph nodes, bone lesions and visceral lesions). Detection of PSMA-positive lesions was separately analyzed for patients with prior or ongoing androgen-deprivation therapy (ADT). Patient with castration-resistant prostate cancer were excluded from the present analysis. In addition, the maximum standardized uptake value (SUV_{max}) and the lesion size were assessed.

^{68}Ga-PSMA-11 PET/MRI

All patients underwent a single injection of ^{68}Ga-PSMA-11 (130 ± 16 MBq, range 90-162 MBq). A clinical routine whole-body PET/MRI was performed 60 min after injection on a hybrid scanner (SIGNA PET/MR, GE Healthcare, Waukesha, WI, USA) used in previous studies at our department (*8*). In brief, the scanner comprises a 3-T MR system with TOF-PET detector ring installed between the body and gradient coils. A 3D dual-echo, spoiled gradient recalled echo sequence (LAVA-FLEX) for AC and a PET emission scan was recorded in list mode. The whole-body protocol included six bed positions with 2 minutes acquisition time each. Specific sequences covering the pelvis, including a high resolution T1-weighted LAVA-FLEX sequence, T2-weighted fast recovery fast spin-echo sequence in two planes and diffusion weighted images (b values: 0, 300, 1000) were acquired with a 15 min PET frame. Furosemide was injected intravenously 30 minutes prior to the ^{68}Ga-PSMA-11

injection (0.13 mg/kg) to reduce halo artifacts (*9*). For attenuation correction an atlas-based MR-AC was used for the head, and for the remaining body air, lung, and soft tissue were segmented using the DIXON LAVA-FLEX sequences generating a fat-water based attenuation correction map. The protocol scan time was 30 minutes.

A dual board-certified radiologist and nuclear medicine physician (R1), incorporating both the MRI and PET information as well as all clinical information, analyzed all images. Furthermore, to investigate interreader variability 2 additional readouts were conducted. For the second read out the following clinical information was given: PSA at scan, stage and grade of primary tumor, surgical margins and Gleason score. Analog to our previous publication only lesions with high suspicion for recurrence were considered positive: focal ^{68}Ga-PSMA-11 uptake in the soft tissue of the prostate bed, lymph nodes with an $SUV_{max} \geq 3$ and/or pathologically increased size ($\geq$ 5 mm for perirectal nodes, $\geq$ 8 mm for iliac / retroperitoneal nodes, $\geq$ 1 cm for inguinal nodes), focal bone uptake with correlating bone marrow replacement or focal uptake with correlating soft tissue lesion (*8*). Most published series suggested values between SUVmax 2-3 as appropriate cut off values, especially for lymph nodes (*10,11*). To minimize false positive interpretation of slightly PSMA positive findings, a cut off of 3 was selected.

Retrospective evaluation of the radiotherapy volume

All scans with ^{68}Ga-PSMA-11 PET/MRI positive lesions were reviewed according to the EORTC and RTOG guidelines (*12,13*). Based on initial tumor stage, nodal status and surgical margins, as well as PSA value, the appropriate radiotherapy target (RT) volume was retrospectively defined based on both guidelines to define the target volume for salvage radiotherapy. If the ^{68}Ga-PSMA-11 PET/MRI positive lesions were located outside a standard salvage radiotherapy volume, a change in RT-volume was given.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25. GraphPad Prism version 7 (PraphPad Software, Inc. La Jolla, USA) was used to generate all images. Intraclass correlation coefficient was used to assess the interreader agreement. Ninety-five percent confidence intervals (CIs) are reported for kappa (κ) values. Interpretation of κ and ICC was based on

a classification established by Landis and Koch: poor 0.0, slight 0.0 - 0.20, fair 0.21 - 0.40, moderate 0.41 - 0.60, good 0.61 - 0.80 and, almost-perfect 0.81 - 1.00 reproducibility (*14*).

RESULTS

Patient characteristics and ^{68}Ga-PSMA-11 PET/MRI detection rate

In this study, we analyzed 66 patients with BR and low PSA levels ≤ 0.5 ng/ml after primary radical prostatectomy. Patient characteristics are summarized in Table 1.

Information of ^{68}Ga-PSMA-11 PET/MRI detection patterns for all patients is given in Table 2. The overall detection rate was 54.5% including patients with prior or ongoing ADT. Subgroup analysis showed a detection rate of 38.5% in patients with very low PSA (0 < 0.2 ng/ml) and of 65.0% in patients with low PSA (0.2 - 0.5 ng/ml) levels. Excluding patients with prior or ongoing ADT slightly reduced the overall detection rate to 51.6%, as well as the detection rate in the very low PSA 33.3% and low PSA 63.2% subgroup (Figure 1).

Localization of suspicious lesions is shown in Figure 2. Overall, suspicious lesions were found in the prostatic bed (local recurrence) 15.1% (n = 10), in lymph nodes 34.8% (n = 23) and in bones 7.6% (n = 5). In 20 of 23 positive lymph nodes, the maximum short axis was < 8 mm, in 2 cases 8 mm and in one case 1 cm. In the very low PSA subgroup, suspicious local recurrence was found in 15.3% (n = 4), lymph node metastasis in 19.2% (n = 5), and bone metastasis in 7.6% (n = 2) of the cohort (n = 26). In the low PSA subgroup local recurrence was detected in 15% (n = 6), lymph node metastasis in 45% (n = 18) and bone metastasis in 7.5% (n = 3) of the patients. A second analysis was performed with exclusion of all previously reported patients (n = 20) (*8*). In the second analysis, the overall detection rate was 51.1% as well as 35.3% and 60% in the very low and low PSA subgroup, respectively. In addition, we summarized the published literature regarding the detection rate of PSMA-positive lesions in patients with low PSA values ≤ 1.0 ng/ml (Table 3).

Localization of ^{68}Ga-PSMA-11 PET/MRI positive lesions within a standard salvage radiotherapy volume

A re-analysis of all patients with positive findings on ^{68}Ga-PSMA-11 PET/MRI discovered that in 26 of 36 patients (72.2%) with positive lesions at least one lesion would not have been covered by the standard RT-volume. In all 8 patients with previous RT PSMA-positive findings were found outside a standard RT-volume. In 18 of 28 patients without previous RT PSMA-positive lesions outside a standard RT-volume were detected. Overall, ^{68}Ga-PSMA-11 PET/MRI detected PSMA-positive lesions outside a standard RT-volume in 26 of 66 patients (39.4%). An example of an

unexpected bone metastasis that would have changed RT-volume is given in Figure 3. In 4 patients, the PSMA-positive finding would have led to an additional boost to the focal finding, an example is given in Figure 4. Only in 11 patients (16.6%) with PSMA-positive findings neither RT-volume nor dosing would have been changed by ^{68}Ga-PSMA-11 PET/MRI findings.

Overall interreader agreement

Generally, the interreader agreement for all 3 readers was almost perfect (kappa 0.855, CI 0.782-0.907). An almost perfect agreement was also detected for lymph node metastases (0.914, CI 0.870-0.94), for local recurrence (0.903, CI 0.855-0.938) and for bone metastases (0.851, CI 0.776-0.904).

DISCUSSION

In this study, we confirmed the previously reported promising detection rate of ^{68}Ga-PSMA-11 PET/MRI even in patients with PSA values ≤ 0.5 ng/ml. An overall detection rate of 65% was observed in patients with PSA values between 0.2 and 0.5 ng/ml. Even at low PSA values ≤ 0.5 ng/ml only 12.1% of all patients had PSMA-positive recurrent disease limited to the prostatic bed and extrapelvic disease was detected in 13.6% of the cohort. Overall, ^{68}Ga-PSMA-11 PET/MRI would have changed the standard sRT volume in 39.4% of all patients.

Given the improved opportunity of cure performing sRT in patients with PSA values below 0.5 ng/ml, a precise re-staging for patients with BR after radical prostatectomy is of outmost interest. Ceci et al. published the hitherto largest cohort of 138 prospective patients with PSA values between 0.2 and 0.5 ng/ml and found a detection rate of 37.9% using ^{68}Ga-PSMA-11 PET/CT (*15*). In the same PSA range, Rauscher et al. presented a detection rate of 55% in 134 retrospectively analyzed patients (*16*). Farolfi et al. reported an overall detection rate of 34.4% in 119 patients (*17*). In addition, Afshar-Oromieh et al. described a detection rate of 46% in 108 patients (*18*). However, their cohort included not only patients following primary radical prostatectomy, but also following primary radiation therapy, which might influence the detection rate. Others reported only small cohorts including 10 to 24 patients and found detection rates between 36 and 57.9% (*19-22*). In our ^{68}Ga-PSMA-11 PET/MRI cohort, we observed a considerably higher detection rate of 65% in patients presenting with PSA values between 0.2 and 0.5 ng/ml at scan. Published data on the detection rate in patients with even lower PSA values < 0.2 ng/ml is scarce and includes only small patient cohorts (*18,19,22,23*). Reported detection rates for this very low PSA cohort range between 33 and 47.1%. We observed a detection rate of 38.5% for patients with very low PSA values < 0.2 ng/ml.

In our cohort, only 8 of 66 patients (12.1%) were found to have PSMA-positive lesions limited to the prostatic bed. The most common site for PSMA-positive recurrence were lymph nodes. However, only 13% of the PSMA-positive lymph nodes were larger than 8 mm. This is even slightly lower, compared to the published data by Giesel et al. showing that only around 36% of the lymph nodes detected on ^{68}Ga-PSMA-11 PET/CT are pathologically enlarged (*10*).

Besides PSA levels, other factors influencing the detection rate of ^{68}Ga-PSMA-11 PET imaging are currently under investigation. First preclinical data suggest that ADT might increase PSMA expression *in vitro* and *in vivo* (*24-26*). A case study by Hope et al. showed a 7-fold increase of PSMA

uptake in a patient treated for 4 weeks with ADT (*27*). Rauscher et al. published a first investigation trying to define predictors for ^{68}Ga-PSMA-11 PET/CT positivity in a retrospective cohort of 272 patients following radical prostatectomy (*16*). In a multivariate analysis they found that the PSA value at scan (OR: 4.20, 95% CI 1.15–15.37) and concurrent ADT (OR: 9.25, 95% CI 1.17–73.31) are significant independent predictors of ^{68}Ga-PSMA-11 PET/CT positivity. On the other hand, a first prospective trial in 8 patients with serial ^{68}Ga-PSMA-11 PET scans 9, 18 and 28 days after the start of ADT did not confirm the expected transient rise in ^{68}Ga-PSMA-11 uptake (*28*) and a retrospective analysis of 10 patients found that continuous long-term ADT between 42 and 369 days significantly reduced the visibility of castration-sensitive prostate cancer in ^{68}Ga-PSMA-11 PET/CT (*29*). In our cohort, only 4 patients had ongoing or prior ADT at the time of scan. In all these patients, PSMA positive lymph nodes were found, even at very low PSA values. Though, additional investigations need to further elucidate the impact of ADT on the uptake of ^{68}Ga-PSMA-11 in different settings and tumor stages. Apart from the above mentioned factors also PSMA-tracer kinetics seem to impact the detection rate in patients with BR. Newly introduced ^{18}F-PSMA-1007 shows only minimal activity in the urinary tract possibly improving the detection of local recurrence or loco-regional lymph nodes (*30,31*). However, studies directly comparing the detection rate of ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 have not yet been performed.

In addition, a rapidly increasing body of literature investigates the alteration of RT management based on ^{68}Ga-PSMA-11 imaging. However, these are commonly rather small cohorts with a wide PSA range. A change in RT planning or management was described in 50 to 77% of all patients using ^{68}Ga-PSMA-11 PET/CT (*32-34*). In addition, it has been shown that ^{68}Ga-PSMA-11 PET/CT based RT leads to a significant PSA response in patients with biochemical recurrence (*5,6*). In our cohort ^{68}Ga-PSMA-11 PET/MRI positive lesions outside a standard RT-volume were found in more than 70% of all patients with PSMA-positive lesions. However, the impact of targeted RT on cancer-specific survival or time to cancer recurrence is still unknown. Future investigations will need to reveal whether targeted treatment of oligo-metastatic disease based on ^{68}Ga-PSMA-11 PET/MRI improves cancer-specific survival.

A limitation of our study is its retrospective nature leading to an inherent selection bias. Due to retrospective data acquisition there is a lack of clinical information in some patients. Furthermore, the reported patient collective is still relatively small and lacks a comparison to histopathology of PSMA-

positive lesions. However, it is the largest cohort investigating the impact of ^{68}Ga-PSMA-11 PET/MRI in patients with very low PSA values and recurrent prostate cancer

CONCLUSION

Our data confirms that ^{68}Ga-PSMA-11 PET/MRI has a high detection rate for recurrent prostate cancer even at low PSA levels ≤ 0.5 ng/ml. In addition, we show that ^{68}Ga-PSMA-11 PET/MRI detected PSMA-positive lesions outside a standard salvage radiotherapy volume in nearly 40% of all patients.

KEY POINTS

Question: How many PSMA-positive lesions were located outside a standard salvage radiotherapy field within the presented cohort?

Pertinent findings: This retrospective analysis focusing on the detection rate of ^{68}Ga-PSMA-11 PET/MRI in patients with recurrent prostate cancer and low PSA values ≤ 0.5 ng/ml revealed an overall detection rate of 54.5%. Moreover, in 65% of all patients with a PSA between 0.2 - 0.5 ng/ml PSMA-positive lesions were detected, making this imaging modality a promising tool for re-staging of prostate cancer.

Implications for patient care: The results of this study encourage to further investigate the value of ^{68}Ga-PSMA-11 PET/MRI in patients with recurrent prostate cancer and low PSA values.

ETHICAL APPROVAL

This retrospective study was approved by the local ethics committee (BASEC Nr. 2016-02230). All patients gave a written informed general consent for retrospective analysis of their data.

DISCLOSURE

The authors declare that no competing financial interests exist. The Department of Nuclear Medicine holds an institutional Research Contract with GE Healthcare. Authors IAB and PAK have received research grants and speaker honorarium from GE Healthcare. Author IAB received research grants from Swiss Life and speaker honorarium from Bayer Health Care and Astellas Pharma AG. Author MG has received research grants from Varian. Authors BK, JM, ASB, HGS, UM, CDF, SK, MG and DE declare no conflict of interest. No other potential conflicts of interest relevant to this article exist.

ACKNOWLEDGMENTS

The authors acknowledge the technicians Marlena Hofbauer and her team for the excellent work on high quality PET/MRI images. The authors thank the Sick legat and the Iten-Kohaut foundation for their financial support.

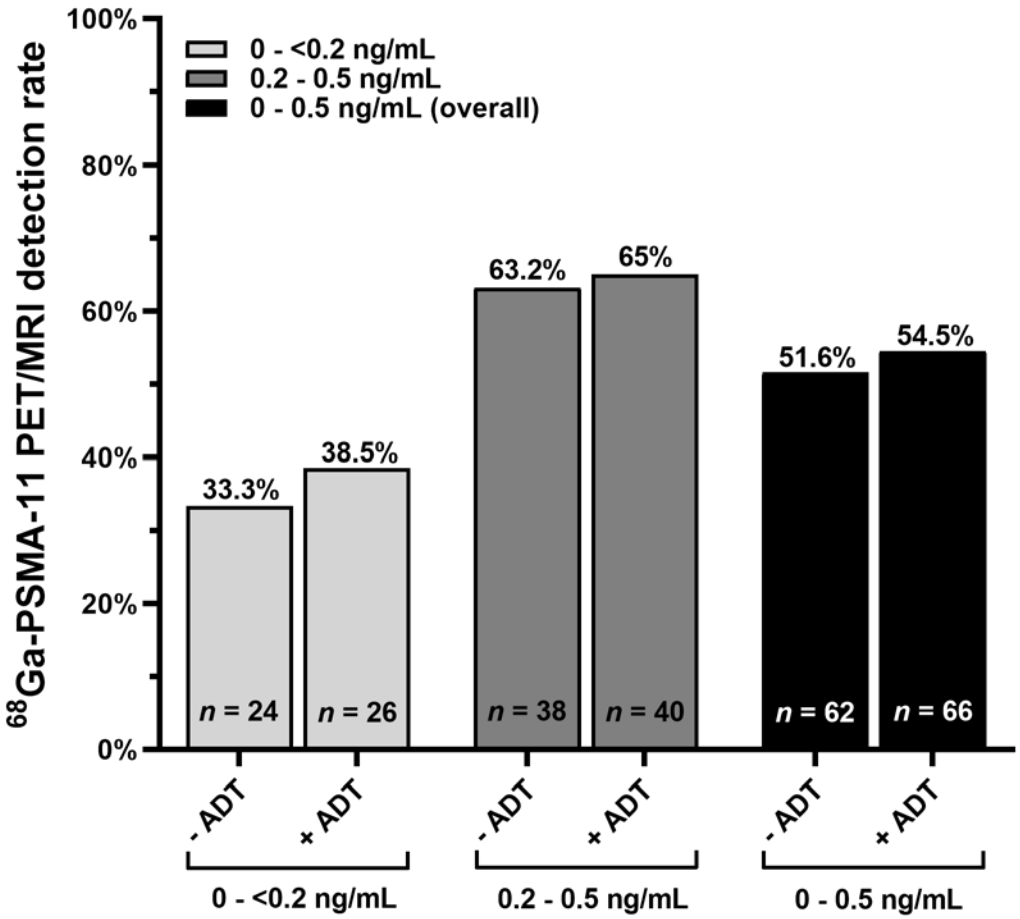

Figure 1: ^{68}Ga-PSMA-11 PET/MRI detection rate stratified by different PSA levels at time of scan. A separate analysis has been performed including patients with ongoing or prior androgen deprivation therapy (ADT). Data is shown as percentage of events.

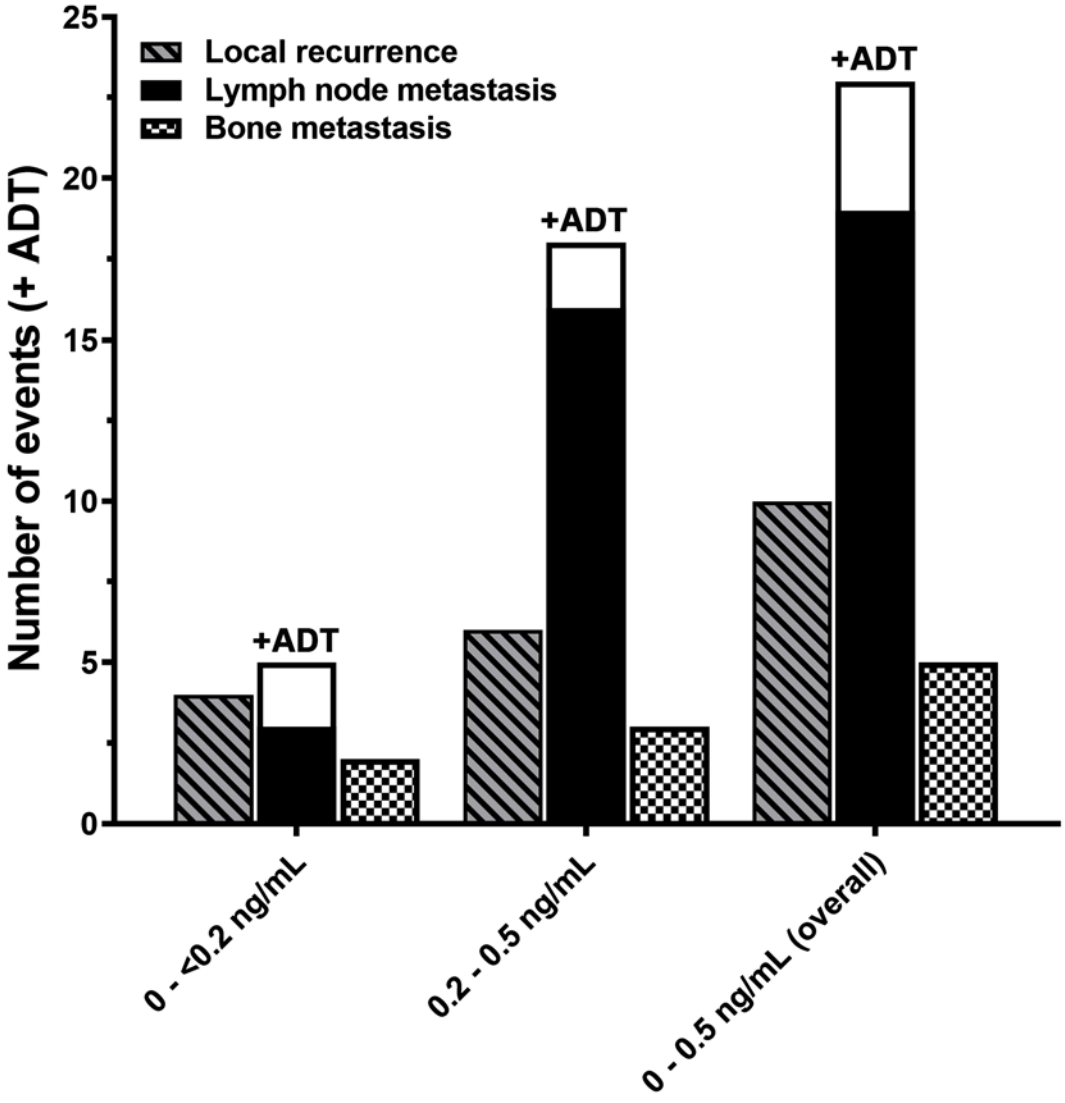

Figure 2: Number of ^{68}Ga-PSMA-11 PET/MRI positive events stratified by localization and PSA levels at time of scan. Androgen deprivation therapy (ADT) prior to the scan increased the detection of positive lymph nodes metastases. Data is shown as total number of events

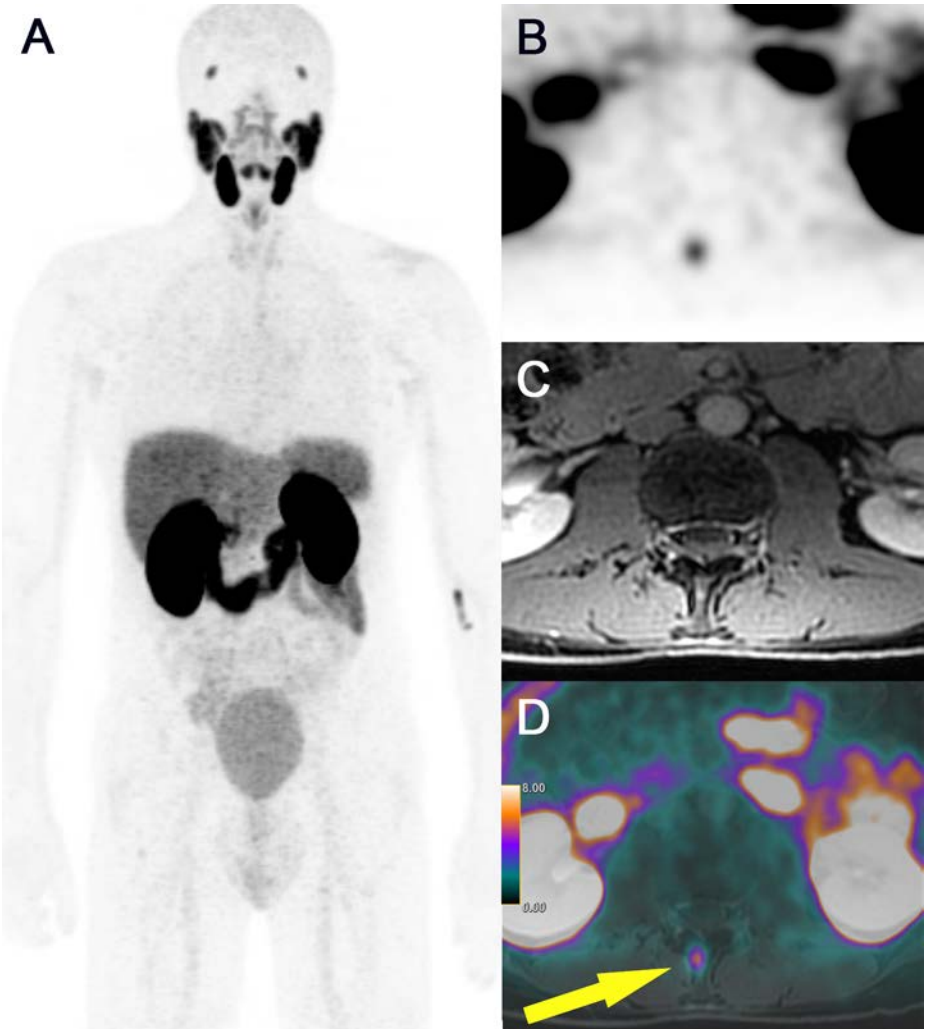

Figure 3: 57-year old patient referred to ^{68}Ga-PSMA-11 PET/MRI after prostatectomy for a pT1c, pN0, cM0, Gleason 7 tumor with a PSA of 0.5 ng/ml. a) There is no focal uptake clearly delineated on the coronal MIP. b) On axial PET a focal uptake in the processus spinosus of the 12th thoracic vertebra was seen (SUV_{max} 5.6), c) corresponding to a minimal contrast enhancing focus on axial post contrast T1-fat sat imaging. d) Correlation is confirmed on the fused images (arrow).

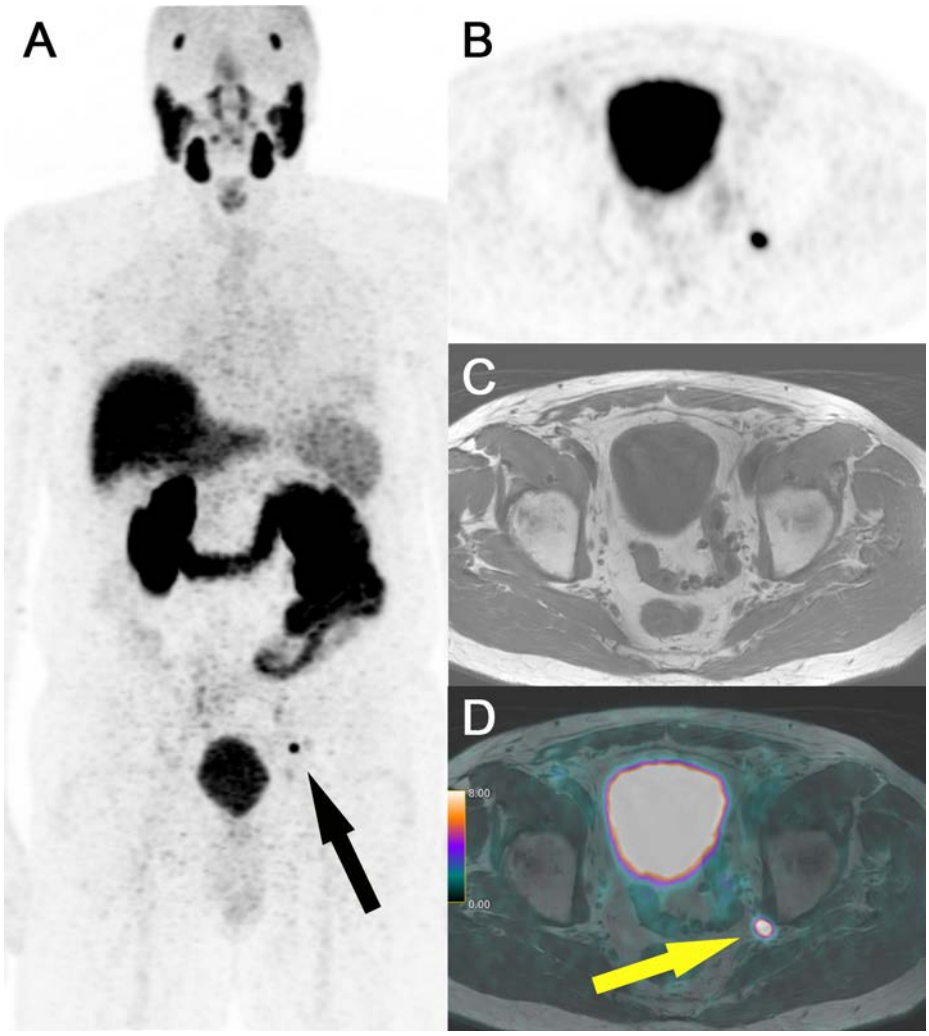

Figure 4: 73-year old patient referred to ^{68}Ga-PSMA-11 PET/MRI after prostatectomy for a pT3a, pN0, cM0 Gleason 7 and a rise in PSA to 0.41 ng/ml 3.5 years after prostatectomy. a) Coronal MIP showed solitary intense focal PSMA-uptake in a left internal iliac area (arrow). b) Focal uptake was confirmed on axial PET (SUV_{max} 23), c) corresponding to a non-enlarged lymph node in the left iliac internal region on axial T1-weighted sequence and d) the fused PET/MRI (arrow). Based on the assessment of our radiation oncologist, this finding would change the radiation plan.

Table 1: Clinical patient characteristics

Characteristics	N = 66	
Age at scan (y)	65	(10)
PSA (ng/ml)		
PSA at initial treatment	8.9	(9.4)
PSA at scan time	0.2	(0.2)
Primary tumor stage (n)		
≤ pT2c	27	(40.9%)
≥ pT3a	34	(51.5%)
n/a	5	(7.6%)
Primary lymph node stage (n)		
pN0	47	(71.2%)
pN1	11	(16.7%)
n/a	8	(12.1%)
Gleason score (n)		
7	36	(54.5%)
8	8	(12.1%)
9	16	(24.2%)
n/a	6	(9.2%)
Resection status (n)		
R0	23	(34.8%)
R1	28	(42.4%)
n/a	15	(22.7%)
ADT		
prior to scan (n)	2	(3.0%)
ongoing at the time of scan (n)	2	(3.0%)
RT		
RT prior to scan (n)	13	(19.7%)

Data presented as median (interquartile range) or number (percent)
ADT: Androgen deprivation therapy, RT: Radiotherapy, n/a: not available

Table 2: Overall detection rate in patients with PSA values ≤ 0.5 ng/ml

Nr	PSA (ng/ml)	ADT	RT	LR	SUV_{max}	LN	SUV_{max}	LN Size (mm)	LN location	BM	SUV_{max}	Dosage (MBq)
1	0.03	**previous**	-	-		+	6.1	3	1	-		138
2	0.05	-	-	-		+	3.9	4	1	-		107
3	0.05	-	-	-		-				-		120
4	0.06	-	-	-		-				-		115
5	0.07	-	-	-		-				-		153
6	0.08	**ongoing**	-	-		+	17.1	4	2	-		90
7	0.08	-	-	-		-				-		114
8	0.08	-	-	-		-				-		115
9	0.09	-	-	-		-				-		146
10	0.1	-	**aRT**	-		-				-		154
11	0.11	-	-	-		-				-		143
12	0.12	-	-	-		-				-		120
13	0.13	-	-	-		-				-		150
14	0.13	-	-	-		-				-		110
15	0.14	-	**sRT**	-		-				+	4.1	113
16	0.14	-	-	+	4	-				-		120
17	0.15	-	**sRT**	-		+	15	8	1	-		126
18	0.15	-	-	+	4.5	-				-		140
19	0.16	-	-	+	5.3	-				+	4.65	126
20	0.16	-	-	+	10.8	-				-		128
21	0.16	-	-	-		-				-		107
22	0.17	-	-	-		-				-		102
23	0.17	-	-	-		-				-		152
24	0.17	-	-	-		-				-		113
25	0.18	-	**sRT**	-		+	12.4	8	1	-		104
26	0.19	-	-	-		-				-		134
27	0.2	**ongoing**	-	-		+	4.1	10	1,2	-		143
28	0.2	-	-	-		+	5	5	2	-		143
29	0.2	-	-	-		-				-		126
30	0.2	-	**sRT**	-		-				-		120
31	0.21	-	**sRT**	-		+	18	4	1	-		121
32	0.22	-	-	-		+	6.4	3	1	-		101
33	0.22	-	-	-		-				-		122
34	0.25	-	-	-		+	25.6	7	1	-		144
35	0.26	-	-	-		-				+	3.9	147
36	0.27	-	**sRT**	-		+	3.7	4	1	-		145
37	0.29	-	-	-		-				-		140
38	0.29	-	-	-		+	2.7	3	1	-		131
39	0.3	-	-	-		-				-		139
40	0.3	-	-	+	9.1	-				-		141
41	0.31	**previous**	**sRT**	-		+	4.9	4	1	-		107
42	0.31	-	-	+	5	-				-		126
43	0.31	-	-	-		-				-		120
44	0.31	-	-	-		-				-		122
45	0.33	-	-	-		-				+	5	137
46	0.33	-	-	-		-				-		136
47	0.34	-	**sRT**	-		+	7.1	6	1	-		108
48	0.34	-	-	-		+	6	3	1	-		152
49	0.34	-	-	-		-				-		137
50	0.36	-	**sRT**	-		-				-		128
51	0.37	-	-	-		-				-		108
52	0.37	-	-	-		-				-		122
53	0.37	-	-	-		-				-		148
54	0.38	-	-	-		+	12.6	5	1	-		147
55	0.4	-	-	+	13.9	-				-		113
56	0.4	-	-	+	4.9	+	4.1	5	1	-		150
57	0.4	-	-	-		+	20	5	1	-		132
58	0.41	-	-	-		+	23.7	7	1	-		135
59	0.45	-	-	-		-				-		142
60	0.45	-	**aRT**	+	13.7	-				-		137
61	0.45	-	-	-		+	9.4	3	1	-		154
62	0.46	-	-	-		+	17.1	6	1, 2	-		122
63	0.49	-	**sRT**	+	4.4	-				-		143
64	0.49	-	-	-		+	5.5	6	1	-		162
65	0.5	-	-	-		+	11.7	5	1	-		140
66	0.5	-	**sRT**	-		-				+	5.6	151

PSA: Prostate Specific Antigen, LR: Local recurrence, LN: Lymph node metastasis, LN: Lymph node, BM: Bone metastasis, SUV_{max}: Maximum Standardized Uptake Value, s/aRT: salvage/adjuvant Radiotherapy, LN location: 1=pelvic, 2=paraaortal, 3=mediastinal/supraclavicular, 4=axillary

Table 3: Reported detection rates in patients with very low PSA values at scan

Author	Year	Imaging modality	*n*	PSA range (ng/ml)	PSMA positive lesions (%)
a) PSA at scan ≤0.5 ng/ml					
Afshar-Oromieh et al. (*18*)	2017	PET/CT	69 108	0 - 0.2 0.21 - 0.5	46 46
Afshar-Oromieh et al. (*19*)	2015	PET/CT	17 10	0 - 0.2 0.21 - 0.5	47.1 50
Caroli et al. (*35*)	2018	PET/CT	n/a	0 - 0.2	27.3
Ceci et al. (*15*)	2019	PET/CT	138	0.2 - 0.5	37.9
Eiber et al. (*20*)	2015	PET/CT	19	0.2 - 0.5	57.9
Farolfi et al. (*17*)	2018	PET/CT	119	0.2 - 0.5	34.4
Hamed etl al. (*21*)	2018	PET/CT	24	0 - <0.5	54.2
Kabaskal et al. (*23*)	2016	PET/CT	12	0 - <0.2	33
Kranzbühler et al. (*8*)	2017	PET/MRI	9 11	0 - 0.2 0.2 - 0.5	44.4 72.7
Morigi et al. (*36*)	2015	PET/CT	16	0 - 0.5	50
Rauscher et al.	2018	PET/CT	134	0.2 – 0.5	55
Schmidt-Hegemann et al. (*22*)	2017	PET/CT	n/a n/a	0 - 0.2 0.21 - 0.5	33.3 41.2
Van Leeuwen et al. (*37*)	2016	PET/CT	13 22 17 11	0.05 - 0.09 0.1 - 0.19 0.2 – 0.29 0.3 – 0.49	8 23 58 36
b) PSA at scan ≤1.0 ng/ml					
Calais et al. (*38*)	2017	PET/CT	270	0 - <1	49
Caroli et al. (*35*)	2018	PET/CT	n/a	0.2 - 1	47.1
Ceci et al. (*15*)	2019	PET/CT	92	0.51 - 1	53.6
Eiber et al. (*20*)	2015	PET/CT	33	0.5 - <1	72.7
Hamed et al. (*21*)	2018	PET/CT	35	0.5 - <1	71.4
Rauscher et al.	2018	PET/CT	138	>0.5 - 1	74
Van Leeuwen et al. (*37*)	2016	PET/CT	7	0.5 – 0.99	57
Verburg et al. (*39*)	2016	PET/CT	27	0 - <1	44

n/a: not available, PSA: prostate-specific antigen

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